

**REMARKS**

The Office Action dated February 10, 2003 presents the examination of claims 1-9, 16-23, and 31-34. Claims 10-15 and 24-30 have been withdrawn from consideration. Claims 2, 10-15, 19-20, and 24-30 are canceled. Claims 1, 3, 4, and 22 are amended. Support for the amendments to the claims is found in the specification. In particular, support for claim 1 is found on page 7, line 13 to page 8, line 13, and support for claim 22 is found on page 18, lines 13-19 of the specification. Claims 3 and 4 are amended to change claim dependencies. Claim 35 is added. Support for the addition of claim 35 is found in original claims 19 and 20. No new matter is inserted into the application.

**Information Disclosure Statement**

An Information Disclosure Statement (IDS) was filed along with the present application on October 23, 2000. The Examiner has not to this date indicated that he has considered the references cited therein. The Examiner is respectfully requested to consider the references, and initial and return the PTO-1449 form as evidence thereof. A copy of the PTO-1449 form is attached to this Reply for the Examiner's convenience.

**Election/Restriction (Paragraph 2, Page 2 of the Office Action)**

The Examiner maintains the Restriction Requirement such that claims 10-15 and 24-30 are withdrawn from consideration. Claims 10-15 and 24-30 are canceled, thus rendering the restriction requirement moot.

**Double Patenting (Paragraph 3, Page 3 of the Office Action)**

The Examiner objects to claims 19 and 20 for being substantial duplicates of claims 22 and 23, respectively. Claims 19 and 20 are canceled, thus rendering the objection moot.

**Rejection under 35 U.S.C. § 102 (Paragraphs 4-5, Pages 3-4 of the Office Action)**

**Barnes '277**

The Examiner rejects claims 1-9, 16-18, 21, and 31-34 under 35 U.S.C. § 102(e) for allegedly being anticipated by Barnes '277 (U.S. Patent 6,410,277). Claim 2 is canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Barnes '277 discloses a formulation of a thermostable or other

DNA polymerase comprising at least one thermostable or other DNA polymerase lacking 3'-exonuclease activity, and at least one thermostable DNA polymerase exhibiting 3'-exonuclease activity. The Examiner asserts that the claims of the present application read on the disclosure of Barnes '277. Applicants respectfully disagree for the following reasons.

First, Barnes '277 fails to disclose a DNA synthesis reaction-enhancer. In other words, although Barnes '277 discloses a thermostable DNA polymerase, Barnes '277 does not disclose that PCR can be improved by adding an acidic macromolecular substance or cationic complex, such as those disclosed in the instant claims 4-9. Furthermore, Barnes '277 does not teach the amended claim 1 simply by disclosing a PCR reaction containing template DNA. Claim 1, as amended, is directed to a DNA synthesis reaction-enhancer comprising at least one kind selected from the group consisting of cationic complexes and acidic macromolecular substances, wherein the acidic macromolecular substance does not serve as a template for subject DNA synthesis. Barnes '277 fails to disclose an acidic macromolecular substance which does not serve as a template for subject DNA synthesis. In other words, although Barnes '277 discloses a PCR reaction containing a DNA template, Barnes '277 fails to disclose a PCR reaction containing a DNA template and an

acidic macromolecular substance which serves as a reaction-enhancer but not as a template for DNA synthesis.

Second, Barnes '277 discloses a formulation and kit comprising at least one thermostable or other DNA polymerase lacking 3'-5' exonuclease activity and at least one thermostable or other DNA polymerase exhibiting 3'-5' exonuclease activity. The object of the Barnes '277 invention is to efficiently catalyze prime extension products of lengths greater than those permitted by conventional formulations, such that mutagenicity generated by the conventional PCR process is reduced. See, column 2, lines 43 to 55 of Barnes '277. Thus, in the invention of Barnes '277, at least one thermostable or other DNA polymerase lacking 3'-5' exonuclease activity plays a role in length extension, while at least one thermostable or other DNA polymerase exhibiting 3'-5' exonuclease activity plays a role in proofreading. Barnes '277 fails to disclose the use of two or more kinds of DNA polymerases each having 3'-5' exonuclease activity which is not reduced, as recited in the amended claim 22, with the object of shortening the DNA synthesis reaction time.

On the other hand, since the DNA synthesis reaction-enhancer of the present invention (as recited in claims 1-9) and/or two or more kinds of DNA polymerases each having 3'-5' exonuclease

activity which is not reduced of the present invention are utilized in a DNA synthesis reaction composition or kit for use in *in vitro* DNA synthesis, an amplified product can be obtained in a shorter reaction time than what is necessary for a conventional PCR or LA-PCR reactions. For example, see Example 5 of the specification.

For all of the above reasons, Barnes '277 fails to anticipate the present invention as recited in the pending claims. Withdrawal of the instant rejection is therefore respectfully requested.

Lee '350

The Examiner also rejects claims 1-9, 16-19, 22, and 31-34 under 35 U.S.C. § 102(e) for allegedly being anticipated by Lee '350 (U.S. Patent 6,495,350). Claims 2 and 19 are canceled, thus rendering the rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Lee '350 discloses compositions and methods for amplifying nucleic acid molecules via one-step/one-tube RT-PCR, using combinations of reverse transcriptase and thermostable DNA polymerases in conjunction with sulfur-containing molecules or acetate-containing molecules. Lee '350 fails to disclose a

reaction-enhancer within the meaning of the instant invention. The Examiner appears to assert that Lee '350 overlaps with the present invention since Lee '350 discloses the use of sulfur-containing molecules or acetate-containing molecules. Applicants respectfully disagree.

Lee '350 discloses that examples of the sulfur-containing molecules include inorganic compounds or low molecular weight organic compounds such as ammonium sulfate, magnesium sulfate, TRIS-sulfate, manganese sulfate or the like, and of the acetate-containing molecules include inorganic compounds or low molecular weight organic compounds such as ammonium acetate, magnesium acetate, TRIS-acetate, manganese acetate or the like. See, for example, column 7, lines 10 to 66. In addition, as described in lines 12 to 3 from the bottom of column 6, the sulfur-containing molecules and acetate-containing molecules are used to relieve RT-mediated (i.e., reverse transcriptase-mediated) inhibition of RT-PCR. In other words, the sulfur-containing molecules and acetate-containing molecules used in the invention of Lee '350 are not DNA synthesis reaction-enhancers.

In addition, since the acidic substance is defined as an acidic macromolecular substance not serving as a template for synthesis of subject DNA in the amended claim 1, the disclosure of

Lee '350 does not overlap with the present invention.

For all of the above reasons, Lee '350 fails to anticipate the present invention as recited in the pending claims. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 103 (Paragraph 6, Pages 4-5 of the Office Action)

The Examiner rejects claims 20 and 23 under 35 U.S.C. § 103(a) for allegedly being obvious over Lee '350 in view of Sorge '580 (U.S. Patent 6,350,580). Claim 20 is canceled, thus rendering the rejection thereof moot. Applicants respectfully traverse the rejection applied to claim 23. Reconsideration of the claim and withdrawal of the instant rejection are respectfully requested.

First, Applicants respectfully point out that Sorge '580 is not prior art to the present invention. The present application has a priority date of April 23, 1998 and a PCT filing date, hence effective U.S. filing date, of April 21, 1999. Sorge '580 was filed on October 11, 2000. Therefore, the rejection over Lee '350 in view of Sorge '580 is improper and should be withdrawn.

Second, Applicants respectfully submit that the present invention is not obvious over Lee '350 alone. As noted above, the sulfur-containing molecules or acetate-containing molecules

disclosed in Lee '350 are utilized to relieve reverse transcriptase-mediated inhibition of RT-PCR. Lee '350 fails to suggest or disclose the use of acidic macromolecular substances for shortening the reaction time of DNA synthesis. As such, the skilled artisan would in no way be motivated to use acidic macromolecular substances for shortening the reaction time of DNA synthesis. For this reason, Lee '350 also fails to render the present invention obvious. Withdrawal of the instant rejection is therefore respectfully requested.

#### Conclusion

Applicants respectfully submit that the above remarks and/or amendments to the instant claims fully address and properly overcome, render moot, or otherwise accommodate all of the pending rejections/objections of record. All of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action on the merits of the present application is thereby requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an



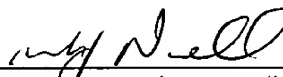
interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of two (2) months to July 10, 2003, in which to file a reply to the Office Action. The required fee of \$410.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Marked up version showing changes made  
PTO Form 1449

**MARKED UP VERSION SHOWING CHANGES MADE**

In the Claims:

Claims 2, 10-15, 19-20, and 24-30 have been canceled.

The claims have been amended as follows:

1. (Amended) A DNA synthesis reaction-enhancer comprising at least one kind selected from the group consisting of [acidic substances and] cationic complexes and acidic macromolecular substances, wherein said acidic macromolecular substances do not serve as templates for subject DNA synthesis.

3. (Amended) The DNA synthesis reaction-enhancer according to claim 1 [2], wherein said acidic macromolecular substance is an acidic polysaccharide.

4. (Twice Amended) The DNA synthesis reaction-enhancer according to claim 3 [2], wherein said acidic macromolecular substance is one or more substances selected from the group consisting of sulfated-fucose-containing polysaccharides, dextran sulfate, carrageenan, heparin, rhamnam sulfate, dermatan sulfate (chondroitin sulfate B), heparan sulfate, hyaluronic acid, alginic

acid, pectin, polyglutamic acids, polyacrylic acids, polyvinyl sulfates, polystyrene sulfates, carrageenan, DNA and salts thereof.

22. (Amended) A DNA synthesis reaction composition comprising two or more kinds of DNA polymerases each having 3'→5' exonuclease activity which is not reduced.

Claim 35 has been added.